EXPRESS MAIL LABEL NO. EV510808507US
DATE OF DEPOSIT: April 21, 2005

IN THE INTERNATIONAL BUREAU OF WIPO

PATENT COOPERATION TREATY
International Bureau

In re International Application of: THE GOVERNMENT OF THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

International Application No.: PCT/US2003/034023

International Filing Date: 24 October 2003 (24.10.2003)

For: METHODS TO PREVENT TUMOR RECURRENCE BY BLOCKADE OF TGF-BETA

Date: November 18, 2004

THE INTERNATIONAL BUREAU OF WIPO
34, CHEMIN DES COLOMBETTES
1211 GENEVA 20
SWITZERLAND

VIA FACSIMILE ONLY
Facsimile No. 41 22 740 1435

AMENDMENTS UNDER ARTICLE 19

Dear Sir or Madam:

Submitted herewith are substitute claims under Article 19, as well as a marked-up version of the claims indicating additions and deletions. Please replace pages 40 to 44 of the international application with the attached replacement pages 40 to 43. Substitute claims 1 through 30 replace original claims 1 through 45. Original claims 2-5, 19, 20, 22-24, 29-31, and 35-37 have been canceled and original claims 1-45 have been renumbered as claims 1-30. Original claims 6, 14-18, 21, 27, 28, 33, 34, 38, and 40-45 have been amended to correct dependency, and original claim 13 has been amended to correct an obvious typographical error.

Original claims 1, 26, and 32 (now new claims 1, 17, and 20) have been amended such that the claims are now directed to a method of inhibiting recurrence of a tumor using an anti-TGF-β monoclonal antibody obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849). Support for these amendments can be found in the specification at least at page 18, lines 25-28, and at page 19, line 23 through page 20, line 15. No new matter has been added by these amendments.

The International Search Report cited two Category "X" references, pertaining to novelty and inventive step. U.S. Patent No. 6,090,383 (Dasch *et al.*) was cited against original claims 1-6, 8-16, 19-21, and 25-37 and, at best, is limited to antibodies (for example the monoclonal antibody 1D11.16) that can be used to i) inhibit TGF-β signaling by blocking

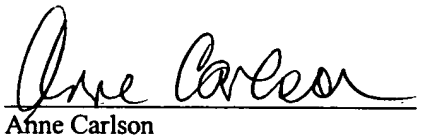
TGF-β from binding to its cell surface receptors, ii) treat *metastatic* cancers, or iii) to inhibit the *growth* of tumors. Dasch *et al* also describes that blocking the TGF-β pathway would lead to tumor *regression*. Mao *et al.* (*Cancer Biotherapy*, 9:317-327, 1994) was cited against original claims 1, 3-4, 8-9, 11, 13-16, 19-21, 26-30, and 32-36. At best, this reference discloses a method of inhibiting tumor growth *in vivo* by administering an anti-TGF-β antibody.

Nowhere in Dasch *et al.* or Mao *et al.* is the word *recurrence* used, nor is there any teaching that an anti-TGF-β antibody can be used to inhibit tumor *recurrence*. Thus, Applicants submit that amended claims 1-30 are both novel and inventive since they each require inhibiting recurrence of a tumor. Applicants request that the International Preliminary Examining Authority take into account the amended claims under Article 19.

Please telephone the undersigned at the telephone number listed below if there are any questions regarding the amended claims.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 
Anne Carlson
Registration No. 47,472

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 228-9446

cc: Docketing

CLAIMS

We claim:

1. A method of inhibiting recurrence of a tumor in a subject, comprising:

administering a therapeutically effective amount of a monoclonal antibody obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849)to the subject in order to block an immunosuppressive effect of transforming growth factor (TGF)-β in the subject, wherein the subject is at risk for recurrence of the tumor, and wherein the monoclonal antibody is specific for TGF-β and neutralizes an activity of TGF-β, thereby inhibiting recurrence of the tumor in the subject.

2. The method of claim 1, wherein the monoclonal antibody inhibits TGF-β from binding a TGF-β receptor.

3. The method of claim 1, wherein the subject is a human.

4. The method of claim 1, wherein the tumor is benign or malignant.

5. The method of claim 1, wherein the tumor comprises a carcinoma, a sarcoma, a leukemia, a lymphoma, or a tumor of the nervous system.

6. The method of claim 1, wherein the tumor comprises a breast tumor, a liver tumor, a pancreatic tumor, a gastrointestinal tumor, a colon tumor a uterine tumor, a ovarian tumor, a cervical tumor, a testicular tumor, a brain tumor, a skin tumor, a melanoma, a retinal tumor, a lung tumor, a kidney tumor, a bone tumor, a prostate tumor, a nasopharygeal tumor, a thryoid tumor, a leukemia, or a lymphoma.

7. The method of claim 1, wherein the agent is administered intravenously, subcutaneously, intradermally, or intramuscularly.

8. The method of claim 1, wherein administering the therapeutically effective amount of the agent results in a lack of tumor growth *in vivo* or *in vitro*.

9. The method of claim 1, wherein blocking the immunosuppressive effect of the TGF-β results in increased immunosurveillance by lymphocytes of the subject.

10. The method of claim 9, wherein the lymphocytes comprise T cells or B cells.

11. The method of claim 9, wherein the lymphocytes include T cells, and the T cells comprise a cytotoxic T lymphocyte (CTL), a $CD8^+$ CTL, a $CD4^+$ cell, a $CD4^+$ CD1d-restricted T cell, an NKT cell, or a combination thereof.

12. The method of claim 9, wherein increased immunosurveillance is measured by an increased biological activity of the lymphocyte.

13. The method of claim 12, wherein the increased activity of the lymphocyte is measured by a CTL assay.

14. The method of claim 13, wherein the CTL assay comprises a chromium release assay.

15. The method of claim 1, wherein the monoclonal antibody inhibits TGF-β receptor signaling.

16. A method of inhibiting recurrence of a tumor in a subject, comprising:

administering a therapeutically effective amount of a monoclonal antibody specific for TGF-β to the subject in order to block an immunosuppressive effect of TGF-β in the subject, wherein the subject is at risk for recurrence of the tumor, and wherein the monoclonal antibody is obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849) and neutralizes an activity of TGF-β, thereby inhibiting recurrence of the tumor in the subject.

17. A method of enhancing an activity of an immune cell to inhibit recurrence of a tumor, comprising:

contacting a TGF-β receptor-expressing immune cell with an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, wherein the monoclonal antibody blocks a TGF-β signaling pathway and wherein blocking the TGF-β signaling pathway results in increased tumor immunosurveillance by the TGF-β receptor-expressing immune cell, thereby enhancing the activity of the immune cell to inhibit recurrence of the tumor.

18. The method of claim 17, wherein the TGF-β receptor-expressing immune cell is a T cell or a B cell.

19. The method of claim 17, wherein the TGF-β receptor-expressing immune cell includes T cells and the T cells comprise a CTL, a $CD8^+$ CTL, a $CD4^+$ cell, a $CD4^+$ CD1d-restricted T cell, or an NKT cell.

20. A method of enhancing an immune response in a subject to inhibit recurrence of a tumor, comprising:

administering to the subject a therapeutically effective amount of an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, wherein the monoclonal antibody blocks a TGF-β signaling pathway and wherein blocking the TGF-β signaling pathway results in increased tumor immunosurveillance in the subject, thereby enhancing the immune response in the subject to inhibit recurrence of a tumor.

21. The method of claim 20, wherein the immune response is a T cell response.

22. The method of claim 21, wherein the T cell response comprises a CTL response, a $CD8^+$ CTL response, a $CD4^+$ T cell response, a $CD4^+$ CD1d-restricted T cell response or an NKT cell response.

23. The method of claim 20, wherein the subject is a human.

24. A method for screening for an agent that inhibits tumor recurrence, comprising:

contacting a TGF-β receptor-expressing immune cell with TGF-β;

contacting the TGF-β receptor-expressing immune cell with an agent; and

assaying for a decrease in activity of TGF-β signaling in the TGF-β receptor-expressing immune cell, as compared to a TGF-β receptor-expressing control immune cell, wherein the control immune cell is not contacted with the agent, thereby screening for an agent that inhibits tumor recurrence.

25. The method of claim 24, further comprising assaying for an increase in activity of the TGF-β receptor-expressing immune cell.

26. The method of claim 24, wherein the TGF-β receptor-expressing immune cell is a CTL.

27. The method of claim 26, wherein the increase in activity of the CTL is measured by a CTL assay.

28. The method of claim 24, wherein the decrease in activity of TGF-β signaling comprises decreased phosphorylation of a Smad protein, decreased nuclear translocation of a Smad protein, or decreased DNA binding of a Smad complex.

29. The method of claim 25, wherein the increase in activity of the TGF-β receptor-expressing immune cell comprises increased immunosurveillance.

30. The method of claim 29, wherein increased immunosurveillance comprises increased CTL activity.

CLAIMS

We claim:

1. A method of inhibiting recurrence of a tumor in a subject, comprising:

administering a therapeutically effective amount of a monoclonal antibody obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849)~~an agent~~ to the subject in order to block an immunosuppressive effect of transforming growth factor (TGF)-β in the subject, wherein the subject is at risk for recurrence of the tumor, and wherein the ~~agent~~ monoclonal antibody is specific for TGF-β and neutralizes an activity of TGF-β, thereby inhibiting recurrence of the tumor in the subject.

2. (Canceled) ~~The method of claim 1, wherein the agent is a monoclonal antibody specific for TGF-β and wherein the monoclonal antibody is obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849).~~

3. (Canceled) ~~The method of claim 1, wherein the agent comprises an antagonist, an antibody, a chemical compound, a small molecule, a peptide mimetic, a peptide, or a protein.~~

4. (Canceled) ~~The method of claim 3, wherein the agent comprises an antibody and wherein the antibody is a polyclonal antibody or a monoclonal antibody.~~

5. (Canceled) ~~The method of claim 4, wherein the monoclonal antibody is specific for a TGF-β.~~

6. (Amended) The method of claim ~~5~~1, wherein the ~~anti TGF-β~~ monoclonal antibody inhibits TGF-β from binding a TGF-β receptor.

7. The method of claim 1, wherein the subject is a human.

8. The method of claim 1, wherein the tumor is benign or malignant.

9. The method of claim 1, wherein the tumor comprises a carcinoma, a sarcoma, a leukemia, a lymphoma, or a tumor of the nervous system.

10. The method of claim 1, wherein the tumor comprises a breast tumor, a liver tumor, a pancreatic tumor, a gastrointestinal tumor, a colon tumor a uterine tumor, a ovarian tumor, a cervical tumor, a testicular tumor, a brain tumor, a skin tumor, a melanoma, a retinal tumor, a lung

tumor, a kidney tumor, a bone tumor, a prostate tumor, a nasopharygeal tumor, a thryoid tumor, a leukemia, or a lymphoma.

11. The method of claim 1, wherein the agent is administered intravenously, subcutaneously, intradermally, or intramuscularly.

12. The method of claim 1, wherein administering the therapeutically effective amount of the agent results in a lack of tumor growth *in vivo* or *in vitro*.

13. (Amended) The method of claim 1, wherein blocking the immunosuppressive effect of the TGF-~~β~~ β results in increased immunosurveillance by lymphocytes of the subject.

14. The method of claim 13, wherein the lymphocytes comprise T cells or B cells.

15. The method of claim 13, wherein the lymphocytes include T cells, and the T cells comprise a cytotoxic T lymphocyte (CTL), a $CD8^+$ CTL, a $CD4^+$ cell, a $CD4^+$ CD1d-restricted T cell, an NKT cell, or a combination thereof.

16. The method of claim 13, wherein increased immunosurveillance is measured by an increased biological activity of the lymphocyte.

17. The method of claim 16, wherein the increased activity of the lymphocyte is measured by a CTL assay.

18. The method of claim 17, wherein the CTL assay comprises a chromium release assay.

19. (Canceled) ~~The method of claim 1, wherein administering comprises contacting a TGF-β receptor with the agent, thereby neutralizing the activity of the TGF-β.~~

20. (Canceled) ~~The method of claim 19, wherein the agent comprises an antagonist, an antibody, a small molecule, a chemical compound, a peptide mimetic, a peptide or a protein.~~

21. (Amended) The method of claim ~~19~~1, wherein the ~~agent~~ monoclonal antibody inhibits TGF-β receptor signaling.

22. (Canceled) ~~The method of claim 1, wherein administering comprises contacting a downstream signaling molecule of the TGF-β receptor with the agent.~~

23. (Canceled) ~~The method of claim 22, wherein the agent comprises an antagonist, an antibody, a small molecule, a chemical compound, a peptide mimetic, a peptide or a protein.~~

24. (Canceled) ~~The method of claim 22, wherein the downstream signaling molecule comprises a Smad protein or a Smad complex DNA-binding co-factor.~~

25. A method of inhibiting recurrence of a tumor in a subject, comprising:

administering a therapeutically effective amount of a monoclonal antibody specific for TGF-β to the subject in order to block an immunosuppressive effect of TGF-β in the subject, wherein the subject is at risk for recurrence of the tumor, and wherein the monoclonal antibody is obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849) and neutralizes an activity of TGF-β, thereby inhibiting recurrence of the tumor in the subject.

26. (Amended) A method of enhancing an activity of an immune cell to inhibit recurrence of a tumor, comprising:

contacting a TGF-β receptor-expressing immune cell with an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, wherein the monoclonal antibody ~~an agent that~~ blocks a TGF-β signaling pathway; and wherein blocking the TGF-β signaling pathway results in increased tumor immunosurveillance by the TGF-β receptor-expressing immune cell, thereby enhancing the activity of the immune cell to inhibit recurrence of the tumor.

27. The method of claim 26, wherein the TGF-β receptor-expressing immune cell is a T cell or a B cell.

28. The method of claim 26, wherein the TGF-β receptor-expressing immune cell includes T cells and the T cells comprise a CTL, a $CD8^+$ CTL, a $CD4^+$ cell, a $CD4^+$ CD1d-restricted T cell, or an NKT cell.

29. (Canceled) ~~The method of claim 26, wherein the agent comprises an antagonist, an antibody, a small molecule, a chemical compound, a peptide mimetic, a peptide or a protein.~~

30. (Canceled) ~~The method of claim 29, wherein contacting a TGF-β receptor-expressing immune cell with an agent comprises contacting a TGF-β or a TGF-β receptor.~~

31. (Canceled) ~~The method of claim 30, wherein the agent contacting the TGF-β comprises an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849.~~

32. (Amended) A method of enhancing an immune response in a subject to inhibit recurrence of a tumor, comprising:

administering to the subject a therapeutically effective amount of an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, wherein the monoclonal antibody ~~an agent that~~ blocks a TGF-β signaling pathway~~,~~ and wherein blocking the TGF-β signaling pathway results in increased tumor immunosurveillance in the subject, thereby enhancing the immune response in the subject to inhibit recurrence of a tumor.

33. The method of claim 32, wherein the immune response is a T cell response.

34. The method of claim 33, wherein the T cell response comprises a CTL response, a $CD8^+$ CTL response, a $CD4^+$ T cell response, a $CD4^+$ CD1d-restricted T cell response or an NKT cell response.

35. (Canceled) ~~The method of claim 32, wherein the agent comprises an antagonist, an antibody, a small molecule, a chemical compound, a peptide mimetic, a peptide or a protein.~~

36. (Canceled) ~~The method of claim 35, wherein the agent contacts a TGF-β or a TGF-β receptor.~~

37. (Canceled) ~~The method of claim 36, wherein the agent comprises an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849).~~

38. The method of claim 32, wherein the subject is a human.

39. A method for screening for an agent that inhibits tumor recurrence, comprising:

contacting a TGF-β receptor-expressing immune cell with TGF-β;

contacting the TGF-β receptor-expressing immune cell with an agent; and

assaying for a decrease in activity of TGF-β signaling in the TGF-β receptor-expressing immune cell, as compared to a TGF-β receptor-expressing control immune cell, wherein the control immune cell is not contacted with the agent, thereby screening for an agent that inhibits tumor recurrence.

40. The method of claim 39, further comprising assaying for an increase in activity of the TGF-β receptor-expressing immune cell.

41. The method of claim 39, wherein the TGF-β receptor-expressing immune cell is a CTL.

42. The method of claim 41, wherein the increase in activity of the CTL is measured by a CTL assay.

43. The method of claim 39, wherein the decrease in activity of TGF-β signaling comprises decreased phosphorylation of a Smad protein, decreased nuclear translocation of a Smad protein, or decreased DNA binding of a Smad complex.

44. The method of claim 40, wherein the increase in activity of the TGF-β receptor-expressing immune cell comprises increased immunosurveillance.

45. The method of claim 44, wherein increased immunosurveillance comprises increased CTL activity.